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Images in Medicine

A case of 'blue skin' and 'dark urine'

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ABSTRACT

A 60-year-old female presented with a 20-year history of progressive dark bluish discoloration of skin and passage of dark colored urine, painful arthritis and a recent history of invasive ductal carcinoma of right breast. Skin biopsy revealed hyaline material which was Periodic-Acid-Schiff stain positive and Congo-red stain negative, urine analysis revealed dark urine with presence reducing substance and radio-imaging showed intervertebral ossification and joint ankyloses. The patient was managed symptomatically with physiotherapy and acetaminophen on as required basis. This image is reported as a classic case of Alkaptonuria with clinical, histopathological and radio-imaging findings and the presence of invasive ductal breast carcinoma in the same patient.

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Introduction

A 60-year-old female presented with a 20-year history of progressive discoloration of face, hands and feet, passage of dark colored urine with history of painful hip and knee joint, total hip replacement of right side and a recent history of invasive ductal carcinoma of right breast.

Clinical and imaging findings

Skin examination revealed dark bluish discoloration of forehead, malar areas, nose, external ears, sclera, dorsum of hands and feet (Fig. 1). Urine analysis revealed dark discolor-

ation of urine with presence of reducing substance (Fig. 2). Skin biopsy showed epidermal thinning with clefted hyaline like material in superficial dermis, breakdown of dermal collagen with occasional crescentic and vermiform shaped ochre colored fibers. The hyaline material was Periodic-Acid-Schiff stain positive and Congo-red stain negative.

Radio imaging with Plain radiograph and magnetic resonance imaging of spine and pelvis revealed ossification of intervertebral discs, ankyloses of antero-inferior part of right sacroiliac joint with partial ankyloses of lumbar facet joints and a post hip replacement right side status (Fig. 3). Renal function tests and echocardiogram were normal. Based on the clinical presentation, urinalysis, skin biopsy and radio imaging she was diagnosed as a case of alkaptonuria. Quantitative measurements of homogentisic acid in urine were not done.

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Fig. 1 – (a) Face pigmentation on malar areas and nose. (b) Nail pigmentation. (c) Scleral pigmentation. (d) Ochronosis with waxy papules and plaques on dorsum and palmar aspects of hands.

Discussion

Alkaptonuria is a rare, autosomal recessive, metabolic disorder affecting 1 in 250,000 to 1 million people worldwide, while certain communities of Slovakia have a much higher

incidence.^{1,2} First reported in 1584 as “black urine disease”,³ it is caused by a deficiency in homogentisic acid oxidase which results in accumulation and deposition of oxidation and polymerization product of homogentisic acid in cartilage, eyelids, forehead, cheeks, axillae, genital regions, nail beds, buccal mucosa, larynx, tympanic membrane, and tendons.

Fig. 2 – Ochronotic pigment in dermis with evidence of dermal collagen breakdown and periodic acid Schiff stain positive material, PAS 10× with H&E 40× as inset (left). Urinalysis showing positive control in left tube, negative control in middle tube, and test sample showing black discoloration with dark green pigmentation after Benedict's test (right).

Fig. 3 – Bamboo spine appearance on plain radiograph and MRI showing gross osteopenia, narrowed disk spaces with disk calcification, bony ankyloses of vertebral bodies, and sacroiliac joints; calcification of interspinous ligaments, total hip replacement prosthesis on right hip.

Homogentisic acid causes dark coloration of urine and sweat. Arthritis, particularly of the spine and large joints, begins in early adulthood. Other features of this condition include cardiovascular complications with valvular heart disease, aortic stenosis and coronary heart disease, nephrocalcinosis, and prostate calculi. Renal cell carcinoma and carcinoma

prostate have been reported in association with alkaptonuria.^{4,5}

Carcinoma breast has not been reported in association with alkaptonuria in literature to the best of our knowledge.

Diagnosis is based on the clinical presentation, demonstration of ochronotic pigment in skin or affected tissues

with radiological changes. Urinalysis reveals dark/black urine with presence of reducing agent; qualitative homogentisic acid estimation is higher than normal and a mutation analysis that reveals a mutation in the HDG gene mapped to 3q1-23. Management is supportive, with low tyrosine/protein diet not helpful in reducing symptoms and difficult to adhere to in long term. Physiotherapy, pain relief, and joint replacement surgery for physical disabilities are the mainstay of therapy. Nitisinone has shown promise in management of alkaptonuria patients although it is not yet approved for treatment.⁶

The patient was advised regular physiotherapy and acetaminophen on required basis.

Conflicts of interest

The authors have none to declare.

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